

## **Section II (Remarks)**

### **A. Summary of Amendment to the Claims**

By the present Amendment, claims 1, 2, 10, 12, 13, 16, 17, 26, 29 and 30 have been amended and claims 8, 19, 32 and 33 have been cancelled. Claims 11 and 22 were previously cancelled. No new matter within the meaning of 35 U.S.C. §132(a) has been introduced by the foregoing amendments.

Claim 1 has been amended to incorporate the subject matter of claim 8 and in order to maintain consistency with currently amended claims 16-20 and 29-30.

Claims 1, 2, 12, 13, 16, 17, 26, 29 and 20 have been amended to recite “hyaluronic acid sodium salt” in place of “hyaluronic acid salt.”

Claims 16 and 17 have been amended by limitation of the cationic polymer to those particularly mentioned in the description, namely chitosan, collagen and gelatin. In addition, the feature that the nanoparticles are ionically crosslinked has been added to the claims. This portion of the amendment is supported in the specification in the first and last paragraphs of the summary of the invention and the first paragraph of the description of the invention.

Thus, upon entry of the amendments, claims 1-7, 9, 10, 12-18, 20, 21, and 23-31 will be pending, of which claims 1-7, 9, 10, 12-15, 21, and 23-28 are withdrawn from consideration. Claims 16-18, 20 and 29-31 are therefore pending and under examination.

In view of the finality of the February 23, 2010 Office Action and to ensure substantive consideration of this response, a Request for Continued Examination is concurrently submitted herewith, together with payment of the appertaining RCE fees (see *infra*, “CONCLUSION”).

### **B. Double Patenting Rejection**

In the Final Office Action mailed February 23, 2010, the examiner provisionally rejected claims 16-20 and 31 on the ground of nonstatutory obviousness-type double patenting, in view of claims 1-12 of co-pending U.S. Patent Application No. 12/301,835. The present application is commonly owned with U.S. Patent Application No. 12/301,835.

In view of the provisional character of this rejection, applicants respectfully request that the double patenting issue be deferred, until one or both of these applications is determined to be in a condition for allowance.

**C. Rejection Under 35 U.S.C. §112, Second paragraph - Indefiniteness**

In the February 23, 2010 Final Office Action, claims 16-20 and 29-33 were rejected under 35 U.S.C. §112, second paragraph as indefinite for failing to point out and distinctly claim the subject matter which applicants regards as the invention. Applicants respectfully respond as follows.

“The limitation ‘characterized by a stability of at least one month at ambient temperature storage’” was alleged to be indefinite. The examiner’s attention is respectfully drawn to Section I above, in which claims 1, 16 and 26 have been amended. As amended, no claim currently contains the phrase alleged by the examiner to be indefinite. The rejection is moot. Withdrawal of the rejection is respectfully requested.

Additionally the examiner rejected claims 32 and 33 as indefinite, for recitation of “the physical properties of particle size and zeta potential,” where the accepted levels of change are not defined.

By the present Response claims 32 and 33 have been cancelled. The rejection is therefore moot and withdrawal is respectfully requested.

**D. Rejection Under 35 U.S.C. §103**

In the Final Office Action mailed February 23, 2010, the examiner maintained the rejection of claims 16-20 and 29-33 under 35 U.S.C. §103(a), as unpatentable over U.S. Patent Application Publication No. 2003/0170313 (hereinafter “Prokop”) in view of U.S. Patent Application Publication No. 2003/0087877 (hereinafter “Calias et al.”). Applicants respectfully traverse the rejection.

Initially it is noted that claims 19, 32 and 33 have been cancelled by the present response. Accordingly the rejection is addressed herein as applicable to pending claims 16-18, 20 and 29-31.

In previous Office Actions responses, applicants have extensively supported the position that one of skill in the art would not have been motivated to combine Prokop and Calias et al. and, even if the two references were viewed in combination, applicants' claimed nanoparticles are not derivable from the combination of Prokop and Calias et al.

In response the examiner replied that “[i]n order to overcome a *prima facie* case of obviousness, it is incumbent upon the Applicant to provide comparative test evidence that demonstrates unexpected superiority of the claimed compositions versus the closest prior art compositions...” (Office Action mailed February 23, 2010, page 7.) However it is applicants' position that the examiner has not demonstrated a *prima facie* case of obviousness.

A *prima facie* case of obviousness based on the rationale that the invention could have been achieved by “combining prior art elements according to known methods to yield predictable results” is supportable by a showing that “all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art.” See MPEP §2143, citing the U.S. Supreme Court decision in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). The cited combination of Prokop in view of Calias et al. does not show that the combination yielded nothing more than predictable results.

As detailed in MPEP §2143, in order to reject a claim based on combining prior art elements according to known methods to yield predictable results, the examiner must demonstrate predictability of the results. Specifically, the examiner must demonstrate “a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable.” It is further provided in MPEP §2143 that “[i]f any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.” Applicants respectfully assert that one of skill in the art could not have predictably arrived at the presently claimed invention from the combination of Prokop and Calias et al., as argued by the examiner.

As the examiner previously noted, Prokop provides nanoparticles and methods of making nanoparticles, but “Prokop does not disclose the use of salts of hyaluronic acid, such as hyaluronic acid, as suitable anionic components” (Office Action mailed June 23, 2008, p. 5;

emphasis added.) The examiner then cited Calias et al. as “disclos[ing] that hyaluronic acid and any of its salts, such as sodium hyaluronate, carboxymethyl cellulose and sodium alginate are all polyanionic polysaccharides...” (Office Action mailed June 23, 2008, p. 5.)

However, applicants maintain the position that it would not have been obvious to use hyaluronic acid, as described in Calias et al. in the nanoparticles of Prokop. Furthermore, even if one of skill in the art had made the mere combination of elements, the method of making recited in claim 16 provides a nanoparticle with a stability that would have been unexpected from the teachings of Prokop and Calias et al.

One of skill in the art would not have combined the hyaluronic acid of Calias et al. with the nanoparticles of Prokop for reasons detailed in previous responses. In sum, Calias et al. only describe the use of hyaluronic acid as a solid biomaterial over which a therapeutic agent is supported by means of covalent bonds. It is stated throughout Calias et al. that the biopolymer/HA is bound to the therapeutic agent by a disulfide (covalent) bond. (See, e.g., paragraphs [0049], [0050], [0052], [0053], and independent claims 1 and 15.) There is no motivation within Calias et al. that would have led a person of skill in the art to reach the conclusion that hyaluronic acid, a solid material used as support and bonded by covalent bonds to a therapeutic agent, could be used in the nanoparticles of Prokop, in which the components are not in solid form and are bonded by electrostatic interactions.

The examiner is reminded of the impermissible use of hindsight, as confirmed by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), wherein it was provided that a factfinder judging patentability “should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.”

Although Calias et al. discloses a drug delivery system, there is no relationship between the conjugates of Calias et al. and the nanoparticles of Prokop, since conjugates of Calias et al. include different components and present a very different chemical structure. In fact, the term “nanoparticle” is not contained within the disclosure of Calias et al. The properties of a formulation combining the different ingredients of both drug delivery systems would not be predictable, particularly by the method recited in claim 16.

Furthermore, the examiner's attention is respectfully directed to Section I above, in which claims 16 and 17 have been amended. By the above amendments, the "hyaluronic acid salt" has been clarified as a "hyaluronic acid sodium salt," the cationic polymer has been specified as selected from chitosan, collagen and gelatin, the sodium tripolyphosphate is clarified as capable of ionically crosslinking the cationic component and the nanoparticles are characterized as ionically cross-linked by means of the sodium tripolyphosphate.

With regard to Prokop being cited as the primary reference in the rejection of claims 16-18, 20 and 29-33 under 35 U.S.C. §103(a), applicants respectfully submit that Prokop does not provide description of any of hyaluronic acid sodium salt or the cross-linker, which is sodium tripolyphosphate. Prokop only provides use of dextran polyaldehyde, a solution of photocrosslinking polymer (polyvinyl alcohol bearing styrypyridinium group) or  $\gamma$ -glutamyl transferase enzyme as the only possible crosslinking agents (See paragraph [0066] and example 121). Additionally, the crosslinking step carried out in Prokop (See paragraph [0066] and example 12) is performed once the nanoparticles have been formed and isolated.

By contrast, in applicants' claimed invention, as recited in claim 16, the crosslinking is performed during the formation of nanoparticles upon mixture of aqueous solutions since the cross-linker is added to one of the aqueous solutions. This renders the nanoparticulate system of claim 16 with a very different structure and confers nanoparticles with additional differences with respect to nanoparticles of Prokop.

For example, since nanoparticles of Prokop are subjected to crosslinking after their formation, only the surface thereof is cross-linked and the core is a complex (See paragraphs [0014], [0015], and [0016], wherein the formation of a complex between polyanionic and polycationic polymers is described). On the contrary, the structure of nanoparticles of the invention is a uniform and homogeneous matrix wherein the entire matrix is crosslinked, not only at the surface. This allows encapsulating of higher amounts of active ingredients. Accordingly, the process defined in claim 16 provides nanoparticles with not only with different components from the nanoparticles of Prokop, but also with different resulting structure.

As shown in example 4 of the present application and in the additional empirical evidence of the 37 CFR §1.132 Declaration of Dr. Pena filed December 10, 2009, the combination of the particular cationic polymers recited in pending claims 16 and 17 with hyaluronic acid sodium salt

and tripolyphosphate as cross-linker, results in the claimed nanoparticulate system, which has improved and unexpected stability. The nanoparticles have demonstrated stability of at least 4 weeks at 4°C, but even at 25°C. In addition, as pointed out in examples 2 and 3 and tables 2 and 3, the active ingredient encapsulation efficiency is higher than 99%.

The nanoparticles of Prokop, comprising cationic polymers and other anionic polymers and being cross-linked with dextran polyaldehyde, a solution of polyvinyl alcohol bearing styrypyridinium group or  $\gamma$ -glutamyl transferase enzyme (Example 12) have only been shown to be stable for 3 weeks at 4°C. Furthermore, only encapsulation/entrapment efficiency less than 40% was obtained (*See* example 24).

Applicants attempted to duplicate the nanoparticles of Prokop with significant difficulty and were unsuccessful in obtaining the described nanoparticles. Accordingly, comparative results of the nanoparticles of Prokop and the nanoparticles of the claimed invention are not available.

Applicants claimed nanoparticles are crosslinked nanoparticles with improved stability and encapsulation efficiency as compared to the described nanoparticles of Prokop. Applicants' claimed nanoparticles are generated by using the particular components of hyaluronic acid sodium salt as anionic component, chitosan, collagen or gelatin as cationic component and sodium tripolyphosphate as cross-linking agent in the nanoparticles. Such a particular makeup would not have been obvious to one of skill in the art in view of Prokop.

One of skill in the art faced with the problem of developing stable nanoparticles would have not considered the combination of Prokop with Calias et al. since, in addition to the comments mentioned above regarding the use of hyaluronic acid or a salt thereof, Calias et al. provides no mention of the possibility of including cationic polymers and cross-linking agents. In Calias et al., the stability of the system is conferred by the covalent interaction between hyaluronic acid and the active ingredient. Therefore, Calias et al. does not suggest that the components of the nanoparticles of claims 16 and 17 could confer a higher stability to a drug release system in the form of nanoparticles, taking also into account that said nanoparticles were obtained by electrostatic interactions.

Prokop in view of Calias et al. fail to provide any derivative basis for the claimed invention and, additionally, there would have been no logical reason for one of skill in the art to combine such

references. Accordingly, no basis of *prima facie* obviousness of the claimed invention is presented by such cited references.

Based on the foregoing, Prokop in view of Calias et al. fails to provide any logical basis for the nanoparticles recited in claims 16-20 and 29-31. Prokop in view of Calias et al. does not render the claimed invention obvious. Accordingly, withdrawal of the rejection of claims 16-18, 20 and 29-31 under 35 U.S.C. §103 (a) as being obvious over Prokop in light of Calias et al. is respectfully requested.

### CONCLUSION

Based on the foregoing, all of applicants' pending claims 16-18, 20 and 29-31 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing and to responsively issue a Notice of Allowance.

The time for responding to the February 23, 2010 Office Action without extension was set at three months, or May 23, 2010. Applicants hereby request a three month extension of time under 37 CFR § 1.136 to extend the deadline for response to August 23, 2010. Payment of the extension fee of \$1,110.00 specified in 37 C.F.R. § 1.17(a)(3) and the Request for Continued Examination fee of \$810.00 specified in 37 C.F.R. § 1.17(e), as applicable to large entity, is being made by on-line credit card authorization at the time of EFS submission of this Response. Should any additional fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as necessary.

If any issues require further resolution, the examiner is requested to contact the undersigned attorneys at (919) 419-9350 to discuss same.

Respectfully submitted,

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